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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

BALASUBRAMANIAN, VENKATARAMAN

ART UNIT PAPER NUMBER

1624

DATE MAILED: 04/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/660,115	Applicant(s) AXON ET AL.	
	Examiner Venkataraman Balasubramanian	Art Unit 1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 18 January 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1 and 4-23 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1 and 4-23 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicants' response, which included cancellation of claims 2-3, addition of new claims 22-23 and amendment to claims 1, 5, 8, 14-19 and 21, filed on 1/18/2006, is made of record. Claims 1 and 4-23 are now pending.

In view of applicants' response, all 112 second paragraph rejections made in the previous office action have been obviated. However, the following rejections made in the previous office action is maintained.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 20 and 23 are rejected under U.S.C. 112, first paragraph, because the specification while being enabling for treating fibrosis of liver, does not reasonably provide enablement for treating any or all diseases or conditions mediated by TGF β generically embraced in the claim language. The specification does not enable any physician skilled in the art of medicine, to use the invention commensurate in scope with these claims.

The instant compounds are disclosed to have TGF β inhibitory activity and it is recited that the instant compounds are therefore useful in treating any or all diseases including fibroproliferative diseases, treating collagen vascular disorders, treating eye diseases associated with a fibroproliferative condition, venting excessive scarring, treating neurological conditions and other conditions that are targets for TGF β inhibitors

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and in preventing excessive scarring that elicits and accompanies restenosis following coronary angioplasty, cardiac fibrosis occurring after infarction and progressive heart failure, and in hypertensive vasculopathy, and keloid formation or hypertrophic scars occurring during the healing of wounds including surgical wounds and traumatic lacerations. Neurological conditions characterized by TGF/ production include CNS injury after traumatic and hypoxic insults, Alzheimer's disease, and Parkinson's disease. Other conditions that are potential clinical targets for TGF/ inhibitors include myelofibrosis, tissue thickening resulting from radiation treatment, nasal polyposis, polyp surgery, liver cirrhosis, and osteoporosis. Diseases benefited by TGFP inhibition include cardiovascular diseases such as congestive heart failure, dilated cardiomyopathy, myocarditis, or vascular stenosis associated with atherosclerosis, angioplasty treatment, or surgical incisions or mechanical trauma, diseases associated with fibrosis and/or sclerosis, including glomerulonephritis of all etiologies, diabetic nephropathy, and all causes of renal interstitial fibrosis, including hypertension, complications of drug exposure, such as cyclosporin, HIV-associated nephropathy, transplant nephropathy, chronic urethral obstruction; hepatic diseases associated with excessive scarring and progressive sclerosis, including cirrhosis due to all etiologies, disorders of the biliary tree, and hepatic dysfunction attributable to infections such as hepatitis virus or parasites', syndromes associated with pulmonary fibrosis with consequential loss of gas exchange or ability to efficiently move air into and out of the lungs, including adult respiratory distress syndrome, idiopathic pulmonary fibrosis, or pulmonary fibrosis due to infectious or toxic agents such as smoke, chemicals, allergens, or autoimmune

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disease; all collagen vascular disorders of a chronic or persistent nature including progressive systemic sclerosis, polymyositis, scleroderma, dermatomyositis, fascists, or Raynaud's syndrome, or arthritic conditions such as rheumatoid arthritis; eye diseases associated with fibroproliferative states, including proliferative vitreoretinopathy of any etiology or fibrosis associated with ocular surgery such as retinal reattachment, cataract extraction, or drainage procedures of any kind; excessive or hypertrophic scar formation in the dermis occurring during wound healing resulting from trauma or surgical wounds, disorders of the gastrointestinal tract associated with chronic inflammation, such as Crohn's disease or ulcerative colitis or adhesion formation as a result of trauma or surgical wounds, polyposis or states post polyp surgery; chronic scarring of the peritoneum associated with endometriosis, ovarian disease, peritoneal dialysis, or surgical wounds; neurological conditions characterized by TGF β production or enhanced sensitivity to TGF β , including states post-traumatic or hypoxic injury, Alzheimer's disease, and Parkinson's disease; diseases of the joints involving scarring sufficient to impede mobility or produce pain, including states post- mechanical or surgical trauma, osteoarthritis and rheumatoid arthritis; and cancer.etc., for which applicants provide no competent evidence.

It appears that the applicants are asserting that the embraced compounds because of their mode action as TGF β inhibitor that would be useful for all sorts of diseases and cancers. However, the applicants have not provided any competent evidence that the instantly disclosed tests are highly predictive for all the uses disclosed and embraced by the claim language for the intended host. Moreover many if not most

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of diseases such as psoriasis and cancers, autoimmune diseases are very difficult to treat and despite the fact that there are many drugs, which can be used for "inflammatory condition".

The scope of the claims involves millions and millions of compounds of claim 1 as well as the thousand of diseases embraced by the terms proliferative disease, cancer, operating through TGF receptors.

Proliferative disease would include benign tumors, malignant tumors, polyps, lumps, lesions, other pre-cancerous conditions, psoriasis, leukemia, the hyper proliferation of the gastric epithelium caused by the *Helicobacter pylori* infection of ulcers.

Cancer is just an umbrella term. Tumors vary from those so benign that they are never treated to those so virulent that all present therapy is useless.

Inflammation is a process that can take place in virtually any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There is no common mechanism by which all, or even most, inflammations arise. Mediators include bradykinin, serotonin, C3a, C5a, histamine, leukotrienes, cytokines, and many, many others. Accordingly, treatments for inflammation are normally tailored to the particular type of inflammation present, as there is no, and there can be no "magic bullet" against inflammation generally.

The "autoimmune diseases" are a process that can take place in virtually any part of the body. There is a vast range of forms that it can take, causes for the problem,

and biochemical pathways that mediate the inflammatory reaction. There are hundreds such diseases, which have fundamentally different mechanisms and different underlying causes. Thus, the scope of claims is extremely broad.

No compound has ever been found to treat cancers of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "compound" is contrary to our present understanding of oncology. Cecil Textbook of Medicine states, "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed article, page 1004). Different types of cancers affect different organs and have different methods of growth and harm to the body. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally. Note substantiation of utility and its scope is required when utility is "speculative", "sufficiently unusual" or not provided. See *Ex parte Jovanovics*, 211 USPQ 907, 909; *In re Langer* 183 USPQ 288. Also note *Hoffman v. Klaus* 9 USPQ 2d 1657 and *Ex parte Powers* 220 USPQ 925 regarding type of testing needed to support in vivo uses.

Next, applicant's attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 66 FR 1092-1099, 2001 wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed method treating solely based on the inhibitory activity disclosed for the compounds. The state of the art is

indicative of the requirement for undue experimentation. See Gressner et al. Front. Biosci. 7: 793-807 2002 (PubMed Abstract provided).

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: Therapeutic use of the compounds in treating disorders/diseases that require TGF β inhibitory activity.

2) The state of the prior art: Recent publication expressed that the TGF β inhibition effects are unpredictable and are still exploratory. See Gressner et al. cited above.

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use for treating any or all condition of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples: Specification has no working examples to show treating any or all condition and the state of the art is that the effects of TGF β inhibitors are unpredictable.

6) The breadth of the claims: The instant claims embrace any or all proliferative diseases and cancers including those yet to be related to TGF β .

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Thus, factors such as “sufficient working examples”, “the level of skill in the art” and “predictability”, etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of enzyme-inhibitor interactions in general, and the lack of working examples regarding the activity of the claimed compounds towards treating the variety of diseases of the instant claims, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

MPEP §2164.01(a) states, “A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was ‘filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).” That conclusion is clearly justified here and undue experimentation will be required to practice Applicants’ invention.

This rejection is same as made in the previous office action but now includes the newly added dependent claim 23.

Applicants' traversal to overcome this rejection is not persuasive.

First of all, instant claims are based on a mode of action to treat any or all diseases. Instant claims, as recited, are reach through claims. A reach through claim is a claim drawn to a mechanistic, receptor binding or enzymatic functionality in general format and thereby reach through a scope of invention for which they lack adequate written description and enabling disclosure in the specification.

In the instant case, based on the inhibition of TGF β by the instant compounds, instant claims reaches through inhibiting and treating any or all diseases in general and thereby they lack adequate written description and enabling disclosure in the specification.

More specifically, in the instant case, based on the mode of action of instant compounds as inhibitor of TGF β , based on limited assay, it is claimed that inhibiting any or all kinases and treating any or all diseases including any or all cancers in general, which there is no enabling disclosure.

Secondly, applicants have not provided any pertinent reference to support that any or all diseases can be treated based on the instant mode of action.

As noted above, contrary to applicants' urging one trained in the art had to extensively undue experimentation to evaluate which disease is treatable without any guidance from instant specification.

Hence, this rejection is proper and is maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-18, 20, 21 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Cai et al. WO 02/47690 for reasons of record. To repeat:

Cai et al. teaches several pyrimidine compounds, which include compounds, composition and the method of use claimed in the instant claims. See formula I on page 10 and note when A=C, given the same pyrimidine core, all variable groups overlap with those of the instant claims. Especially see formula II and III on page 11-12 which shows the desired pyrimidine compounds. See entire document for the details of the invention. See pages 13-34 for various species of pyrimidine compounds. See pages 139-152 for A Table of compounds. Especially see compound 73, 75, 46 and 20.

This rejection is same as made in the previous office action. Although applicants' amendment excludes aniline compound and indoyl compounds, the reference clearly teaches various indolyl compounds noted by the applicants and in addition, pyrimidinyl pyridinyl (page 22, last five species, page 34, first five species), benzimidazolyl (page 33, last species) compounds. Hence, this rejection is maintained.

Claims 1-18, 20 and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by Davies et al. WO 02/22607.

In view of applicants' amendment, this rejection has been obviated.

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Claims 1-19 are rejected under 35 U.S.C. 102(b) as being anticipated by Kleemann et al. US 5,849,758.

Kleemann et al. teaches several pyrimidine compounds, which include compounds claimed in the instant claims. See formula I on column 1 and note when Z is N, given the same pyrimidine core, and A is aryl or heteroaryl, compounds taught by Kleemann et al include those of the instant claims. See column 1-3 for the details of the invention. See column 3-5 for various species of pyrimidine compounds. See Table X for various compounds, which include instant compounds.

In view of applicants' amendment to exclude O from X definition, this rejection is deemed as obviated.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cai et al., WO 02/47690 for reasons of record and for reasons stated in the above 102 rejection. To repeat:

Teachings of Cai et al. as discussed in the above 102 rejection is incorporated herein. As noted above, Cai et al teaches several pyrimidine compounds which include instant compounds.

Cai et al differ from instant claims in exemplifying only few compounds, which fall in the genus of instant compounds.

However, Cai et al. teaches the equivalency of those compounds exemplified with specific substituents with that generically recited on page 10-12 for Formula I-III. See formula I-III and note the definition of various variable groups include several compounds. Thus, it would have been obvious to one having ordinary skill in the art at the time of the invention was made to make pyrimidine compounds variously substituted with Ar₁, Ar₂, R₁, R₂ and R₃ as permitted by the reference and expect resulting

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compounds (instant compounds) to possess the uses taught by the art in view of the equivalency teaching outline above.

This rejection is same as made in the previous office action but now includes newly added claims. As noted above, applicants' amendment did not overcome this rejection. Hence, this rejection is proper and is maintained.

Claims 1-19 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kleemann et al., US 5,849,758 for reasons of record.

Teachings of Kleemann et al. as discussed in the above 102 rejection is incorporated herein. As noted above, Kleemann et al teaches several pyrimidine compounds which include instant compounds.

Kleemann et al, although exemplifying several compounds, which fall in the genus of instant compounds, does not fully exemplify all compounds embraced in the genus of Formula I. However, Kleemann et al. teaches the equivalency of those compounds exemplified with specific substituents with that generically recited for formula I. See formula I and note the definition of various variable groups include several compounds. Thus, it would have been obvious to one having ordinary skill in the art at the time of the invention was made to make variously substituted pyrimidine compounds as permitted by the reference and expect resulting compounds (instant compounds) to possess the uses taught by the art in view of the equivalency teaching outline above.

This rejection is same as made in the previous office action. Although applicants' amendment to exclude O from X definition obviates the 102 rejection, in view of

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equivalency teaching of X as O with X as S in Kleemann, this rejection is proper and is maintained.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (571) 272-0662. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 6.00 PM. The Supervisory Patent Examiner (SPE) of the art unit 1624 is James O. Wilson, whose telephone number is 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned (571) 273-8300. Any

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inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAG. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-2 17-9197 (toll-free).


Venkataraman Balasubramanian

4/1/2006